TEMOZOLOMIDE- temozolomide capsule
ANI Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TEMOZOLOMIDE CAPSULES safely and effectively. See full prescribing information for TEMOZOLOMIDE CAPSULES.

TEMOZOLOMIDE capsules, for oral use
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Warnings and Precautions (5.5) 11/2019

INDICATIONS AND USAGE

Temozolomide is an alkylating drug indicated for the treatment of adult patients with:

- Newly diagnosed glioblastoma concomitantly with radiotherapy and then as maintenance treatment. (1.1)
- Refractory anaplastic astrocytoma who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine. (1.2)

DOSAGE AND ADMINISTRATION

- Administer capsules orally.
- Newly Diagnosed Glioblastoma:
  - 75 mg/m^2 once daily for 42 days concomitant with focal radiotherapy followed by initial maintenance dose of 150 mg/m^2 once daily for Days 1 to 5 of each 28-day cycle for 6 cycles. May increase maintenance dose to 200 mg/m^2 for cycles 2 - 6 based on toxicity. (2.1)
  - Provide Pneumocystis pneumonia (PCP) prophylaxis during concomitant phase and continue in patients who develop lymphopenia until resolution to grade 1 or less. (2.1)
- Refractory Anaplastic Astrocytoma: Initial dose of 150 mg/m^2 once daily on Days 1 to 5 of each 28-day cycle. (2.2)

DOSAGE FORMS AND STRENGTHS

- 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg capsules. (3)

CONTRAINDICATIONS

- History of hypersensitivity to temozolomide or any other ingredients in temozolomide capsules and dacarbazine. (4)

WARNINGS AND PRECAUTIONS

- Myelosuppression: Monitor absolute neutrophil count (ANC) and platelet count prior to each cycle and during treatment. Geriatric patients and women have a higher risk of developing myelosuppression. (5.1)
- Myelodysplastic Syndrome and Secondary Malignancies, including myeloid leukemia, have been observed. (5.2)
- *Pneumocystis* pneumonia (PCP): Closely monitor all patients, particularly those receiving steroids, for the development of lymphopenia and PCP. (5.3)
- Hepatotoxicity: Fatal and severe hepatotoxicity have been reported. Perform liver tests at baseline, midway through the first cycle, prior to each subsequent cycle, and approximately two to four weeks after the last dose of temozolomide capsules. (5.4)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. Advise male patients with pregnant partners or female partners of reproductive potential to use condoms. (5.5, 8.1, 8.3)

ADVERSE REACTIONS

- The most common adverse reactions (≥20% incidence) are: alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia, and convulsions. (6.1)
- The most common Grade 3 to 4 hematologic laboratory abnormalities (≥10% incidence) in patients with anaplastic astrocytoma are: decreased lymphocytes, decreased platelets, decreased neutrophils, and decreased leukocytes.

(6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amerigen Pharmaceuticals, Ltd. at 1-877-220-3784 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Newly Diagnosed Glioblastoma

Temozolomide capsules are indicated for the treatment of adult patients with newly diagnosed glioblastoma concomitantly with radiotherapy and then as maintenance treatment.

1.2 Refractory Anaplastic Astrocytoma

Temozolomide capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Dosage Modifications for Newly Diagnosed Glioblastoma

Administer temozolomide capsules once daily for 42 consecutive days during the concomitant phase with focal radiotherapy and then once daily on Days 1 to 5 of each 28-day cycle for 6 cycles during the maintenance phase.

Provide *Pneumocystis* pneumonia (PCP) prophylaxis during the concomitant phase and continue in patients who develop lymphocytopenia until resolution to grade 1 or less *[see Warnings and Precautions (5.3)]*.

Concomitant Phase

The recommended dosage of temozolomide capsules is 75 mg/m^2 orally once daily for 42 days (up to 49 days) concomitant with focal radiotherapy (60 Gy administered in 30 fractions). Focal radiotherapy includes the tumor bed or resection site with a 2- to 3-cm margin.

Obtain a complete blood count weekly. No dose reductions are recommended during the concomitant phase. The recommended dosage modifications during the concomitant phase are provided in **Table 1**.

TABLE 1: Temozolomide Dosage Modifications During Concomitant Phase

Adverse Reaction	Interruption*	Discontinuation
Absolute Neutrophil Count	Withhold temozolomide capsules if ANC is greater than or equal to 0.5 x 10^9/L and less than 1.5 x 10^9/L. Resume temozolomide capsules when ANC is greater than or equal to 1.5 x 10^9/L.	Discontinue temozolomide capsules if platelet count is less than 0.5 x 10^9/L.
Platelet Count	Withhold temozolomide capsules if platelet count is greater than or equal to 10 x 10^9/L and less than	Discontinue temozolomide capsules if platelet count is less than 10 x 10^9/L.

	100 x 10^9/L. Resume temozolomide capsules when platelet count is greater than or equal to 100 x 10^9/L.	
Nonhematological Adverse Reaction (except for alopecia, nausea, vomiting)	Withhold temozolomide capsules if Grade 2 adverse reaction occurs. Resume temozolomide capsules when resolution to Grade 1 or less.	Discontinue temozolomide capsules if Grade 3 or 4 adverse reaction occurs.

Maintenance Phase

Beginning 4 weeks after Concomitant Phase completion, administer temozolomide capsules orally once daily on Days 1 to 5 of each 28-day cycle for 6 cycles. The recommended dosage of temozolomide capsules is as follows:

- Cycle 1: 150 mg/m^2 per day
- Cycles 2 to 6: May increase to 200 mg/m^2 per day if the following conditions are met before starting cycle 2. If the dose was not escalated at the onset of Cycle 2, **do not** increase the dose for Cycles 3 to 6.
    - Nonhematologic toxicity is grade 2 or less (except for alopecia, nausea, and vomiting)
    - ANC is greater than or equal to 1.5 x 10^9/L and
    - Platelet count is greater than or equal to 100 x 10^9/L.

Obtain a complete blood count on Day 22 and then weekly until the ANC is above 1.5 x 10^9/L and the platelet count is above 100 x 10^9/L. Do not start the next cycle until the ANC and platelet count exceed these levels.

The recommended dosage modifications during the maintenance phase are provided in **Table 2**. If temozolomide capsules are withheld, reduce the dose for the next cycle by 50 mg/m^2 per day. Permanently discontinue temozolomide capsules in patients who are unable to tolerate a dose of 100 mg/m^2 per day.

TABLE 2: Temozolomide Dosage Modifications During Maintenance Treatment

Toxicity	Interruption and Dose Reduction	Discontinuation
Absolute Neutrophil Count	Withhold temozolomide capsules if ANC is less than 1 x 10^9/L. When ANC is above 1.5 x 10^9/L, resume temozolomide capsules at reduced dose for the next cycle.	Unable to tolerate a dose of 100 mg/m^2 per day.
Platelet Count	Withhold temozolomide capsules if platelet count is less than 50 x 10^9/L. When platelet count is above 100	Unable to tolerate a dose of 100 mg/m^2 per day.

	x 10^9/L, resume temozolomide capsules at reduced dose for the next cycle.	
Nonhematological Adverse Reaction (except for alopecia, nausea, vomiting)	Withhold temozolomide capsules if Grade 3 adverse reaction. When resolved to grade 1 or less, resume temozolomide capsules at reduced dose for the next cycle.	Recurrent Grade 3 after dose reduction. Grade 4 Unable to tolerate a dose of 100 mg/m^2 per day.

2.2 Recommended Dosage and Dosage Modifications for Refractory Anaplastic Astrocytoma

The recommended initial dosage of temozolomide capsules is 150 mg/m^2 once daily on Days 1 to 5 of each 28-day cycle. Increase the temozolomide capsule dose to 200 mg/m^2 per day if the following conditions are met at the nadir and on Day 1 of the next cycle:

- ANC is greater than or equal to 1.5 x 10^9/L and
- Platelet count is greater than or equal to 100 x 10^9/L

Continue temozolomide capsules until disease progression or unacceptable toxicity. In the clinical trial, treatment could be continued for a maximum of 2 years, but the optimum duration of therapy is not known.

Obtain a complete blood count on Day 22 and then weekly until the ANC is above 1.5 x 10^9/L and the platelet count is above 100 x 10^9/L. Do not start the next cycle until the ANC and platelet count exceed these levels.

If the ANC is less than 1 x 10^9/L or the platelet count is less than 50 x 10^9/L during any cycle, reduce the temozolomide capsule dose for the next cycle by 50 mg/m^2 per day. Permanently discontinue temozolomide capsules in patients who are unable to tolerate a dose of 100 mg/m^2 per day.

2.3 Preparation and Administration

Temozolomide is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

Administer temozolomide capsules consistently with respect to food (fasting vs. nonfasting) *[see Clinical Pharmacology (12.3)]*. To reduce nausea and vomiting, take temozolomide capsules on an empty stomach or at bedtime and consider antiemetic therapy prior to and/or following temozolomide capsules administration.

Swallow temozolomide capsules whole. Do not open or chew capsules.

If capsules are accidentally opened or damaged, take precautions to avoid inhalation or contact with the skin or mucous membranes. In case of powder contact, the hands should be washed.

3 DOSAGE FORMS AND STRENGTHS

- Temozolomide capsules, 5 mg, have a green opaque cap and white opaque body. The capsule is imprinted with “AMG” on the cap and “252” on the body in black ink.
- Temozolomide capsules, 20 mg, have a gold cap and white opaque body. The capsule is imprinted with “AMG” on the cap and “253” on the body in black ink.
- Temozolomide capsules, 100 mg, have a pink opaque cap and white opaque body. The capsule is imprinted with “AMG” on the cap and “254” on the body in black ink.
- Temozolomide capsules, 140 mg, have a blue cap and white opaque body. The capsule is

imprinted with “AMG” on the cap and “255” on the body in black ink.
- Temozolomide capsules, 180 mg, have a dark orange opaque cap and white opaque body. The capsule is imprinted with “AMG” on the cap and “256” on the body in black ink.
- Temozolomide capsules, 250 mg, have a white opaque cap and body. The capsule is imprinted with “AMG” on the cap and “257” on the body in black ink.

4 CONTRAINDICATIONS

Temozolomide capsules are contraindicated in patients with a history of hypersensitivity reactions to:

- Temozolomide or any other ingredients in temozolomide capsules; and
- dacarbazine, since both temozolomide and dacarbazine are metabolized to the same active metabolite 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide.

Reactions to temozolomide capsules have included anaphylaxis *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Myelosuppression, including pancytopenia, leukopenia and anemia, some with fatal outcomes, have occurred with temozolomide capsules *[see Adverse Reactions (6.1, 6.2)]*. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression.

Prior to dosing, patients must have an ANC of 1.5 x 10^9/L or greater and a platelet count of 100 x 10^9/L or greater.

For the concomitant phase with radiotherapy, obtain a complete blood count prior to initiation of treatment and weekly during treatment *[see Dosage and Administration (2.1)]*.

For the 28-day treatment cycles, obtain a complete blood count prior to treatment on Day 1 and on Day 22 of each cycle. Perform complete blood counts weekly until recovery if the ANC falls below 1.5 x 10^9/L and the platelet count falls below 100 x 10^9/L *[see Dosage and Administration (2.1, 2.2)]*.

5.2 Myelodysplastic Syndrome and Secondary Malignancies

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been observed following temozolomide capsule administration.

5.3 *Pneumocystis* Pneumonia

Pneumocystis pneumonia (PCP) can occur in patients receiving temozolomide capsules. The risk of PCP is increased in patients receiving steroids or with longer treatment regimens.

For patients with newly diagnosed glioblastoma, provide PCP prophylaxis for all patients during the concomitant phase. Continue in patients who experience lymphopenia until resolution to grade 1 or less *[see Dosage and Administration (2.1)]*.

Monitor all patients receiving temozolomide capsules for the development of lymphopenia and PCP.

5.4 Hepatotoxicity

Fatal and severe hepatotoxicity have been reported in patients receiving temozolomide. Perform liver tests at baseline, midway through the first cycle, prior to each subsequent cycle, and approximately two to four weeks after the last dose of temozolomide.

5.5 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, temozolomide capsules can cause fetal harm when administered to a pregnant woman. Adverse developmental outcomes have been reported in both pregnant patients and pregnant partners of male patients. Oral administration of temozolomide to rats and rabbits during the period of organogenesis resulted in embryolethality and polymalformations at doses less than the maximum human dose based on body surface area.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with temozolomide capsules and for at least 6 months after the final dose. Because of potential risk of genotoxic effects on sperm, advise male patients with female partners of reproductive potential to use condoms during treatment with temozolomide capsules and for at least 3 months after the final dose. Advise male patients not to donate semen during treatment with temozolomide capsules and for at least 3 months after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression *[see Warnings and Precautions (5.1)]*.
- Myelodysplastic Syndrome and Secondary Malignancies *[see Warnings and Precautions (5.2)]*.
- Pneumocystis Pneumonia *[see Warnings and Precautions (5.3)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Newly Diagnosed Glioblastoma

The safety of temozolomide was evaluated in Study MK-7365-051 *[see Clinical Studies (14.1)]*.

Forty-nine percent (49%) of patients treated with temozolomide reported one or more severe or life-threatening reactions, most commonly fatigue (13%), convulsions (6%), headache (5%), and thrombocytopenia (5%).

The most common adverse reactions (≥20%) across the cumulative temozolomide experience were alopecia, fatigue, nausea, and vomiting. **Table 3** summarizes the adverse reactions in Newly Diagnosed Glioblastoma Trial. Overall, the pattern of reactions during the maintenance phase was consistent with the known safety profile of temozolomide.

TABLE 3: Adverse Reactions (≥5%) in Patients Receiving Temozolomide Capsules in Newly Diagnosed Glioblastoma Trial

	Concomitant Phase				**Maintenance Phase**	
	Radiation Therapy and Temozolomide N=288*		**Radiation Therapy Alone N=285**		**Temozolomide N=224**	
Adverse Reactions	**All Grades (%)**	**Grade ≥3 (%)**	**All Grades (%)**	**Grades ≥3 (%)**	**All Grades (%)**	**Grade ≥3 (%)**
Skin and Subcutaneous Tissue						

Alopecia	69		63		55	
Rash	19	1	15		13	1
Dry Skin	2		2		5	<1
Pruritus	4		1		5	
Erythema	5		5		1	
General						
Fatigue	54	7	49	5	61	9
Anorexia	19	1	9	<1	27	1
Headache	19	2	17	4	23	4
Weakness	3	2	3	1	7	2
Dizziness	4	1	4		5	
Gastrointestinal System						
Nausea	36	1	16	<1	49	1
Vomiting	20	<1	6	<1	29	2
Constipation	18	1	6		22	
Diarrhea	6		3		10	1
Stomatitis	7		5	<1	9	1
Abdominal Pain	2	<1	1		5	<1
Eye						
Vision Blurred	9	1	9	1	8	
Injury						
Radiation Injury NOS	7		4	<1	2	
Central and Peripheral Nervous System						
Convulsions	6	3	7	3	11	3
Memory Impairment	3	<1	4	<1	7	1
Confusion	4	1	4	2	5	2
Special Senses Other						
Taste Perversion	6		2		5	
Respiratory System						
Coughing	5	1	1		8	<1
Dyspnea	4	2	3	1	5	<1
Psychiatric						
Insomnia	5		3	<1	4	
Immune System						
Allergic Reaction	5		2	<1	3	
Platelet, Bleeding and Clotting						
Thrombocytopenia	4	3	1		8	4
Musculoskeletal System						
Arthralgia	2	<1	1		6	

*One patient who was randomized to radiation therapy only arm received radiation therapy and temozolomide.
NOS=not otherwise specified.
Note: Grade 5 (fatal) adverse reactions are included in the Grade ≥3 column.

When laboratory abnormalities and adverse reactions were combined, Grade 3 or Grade 4 neutrophil abnormalities including neutropenic reactions were observed in 8% of patients, and Grade 3 or Grade 4

platelet abnormalities including thrombocytopenic reactions, were observed in 14% of patients.

Refractory Anaplastic Astrocytoma

The safety of temozolomide was evaluated in Study MK-7365-006 *[see Clinical Studies (14.2)]*.

Myelosuppression (thrombocytopenia and neutropenia) was the dose-limiting adverse reaction. It usually occurred within the first few cycles of therapy and was not cumulative. Myelosuppression occurred late in the treatment cycle and returned to normal, on average, within 14 days of nadir counts. The median nadirs occurred at 26 days for platelets (range: 21-40 days) and 28 days for neutrophils (range: 1-44 days). Only 14% (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a platelet nadir, which may have delayed the start of the next cycle. Less than 10% of patients required hospitalization, blood transfusion, or discontinuation of therapy due to myelosuppression.

The most common adverse reactions (≥20%) were nausea, vomiting, headache, fatigue, constipation, and convulsions.

Tables 4 and **5** summarize the adverse reactions and hematological laboratory abnormalities in Refractory Anaplastic Astrocytoma Trial.

TABLE 4: Adverse Reactions (≥5%) in Patients Receiving Temozolomide in Refractory Anaplastic Astrocytoma Trial

	Temozolomide N=158	
Adverse Reactions	**All Reactions (%)**	**Grade 3-4 (%)**
Gastrointestinal System		
Nausea	53	10
Vomiting	42	6
Constipation	33	1
Diarrhea	16	2
Abdominal pain	9	1
Anorexia	9	1
General		
Headache	41	6
Fatigue	34	4
Asthenia	13	6
Fever	13	2
Back pain	8	3
Central and Peripheral Nervous System		
Convulsions	23	5
Hemiparesis	18	6
Dizziness	12	1
Coordination abnormal	11	1
Amnesia	10	4
Insomnia	10	
Paresthesia	9	1
Somnolence	9	3
Paresis	8	3
Urinary incontinence	8	2
Ataxia	8	2
Dysphasia	7	1

Convulsions local	6	
Gait abnormal	6	1
Confusion	5	
Cardiovascular		
Edema peripheral	11	1
Resistance Mechanism		
Infection viral	11	
Endocrine		
Adrenal hypercorticism	8	
Respiratory System		
Upper respiratory tract infection	8	
Pharyngitis	8	
Sinusitis	6	
Coughing	5	
Skin and Appendages		
Rash	8	
Pruritus	8	1
Urinary System		
Urinary tract infection	8	
Micturition increased frequency	6	
Psychiatric		
Anxiety	7	1
Depression	6	
Reproductive Disorders		
Breast pain, female	6	
Metabolic		
Weight increase	5	
Musculoskeletal System		
Myalgia	5	
Vision		
Diplopia	5	
Vision abnormal*	5	

*This term includes blurred vision; visual deficit; vision changes; and vision troubles.

TABLE 5: Grade 3 to 4 Adverse Hematologic Laboratory Abnormalities in Refractory Anaplastic Astrocytoma Trial

	Temozolomide*,†
Decreased lymphocytes	55%
Decreased platelets	19%
Decreased neutrophils	14%
Decreased leukocytes	11%
Decreased hemoglobin	4%

*Change from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.
†Denominator range = 142, 158

Hematological Toxicities for Advanced Gliomas

In clinical trial experience with 110 to 111 females and 169 to 174 males (depending on measurements), females experienced higher rates of Grade 4 neutropenia (ANC < 0.5 x 10^9/L) and thrombocytopenia (< 20 x 10^9/L) than males in the first cycle of therapy (12% vs. 5% and 9% vs. 3%, respectively).

In the entire safety database for which hematologic data exist (N=932), 7% (4/61) and 9.5% (6/63) of patients > 70 years experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. For patients ≤ 70 years, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. Pancytopenia, leukopenia, and anemia also occurred.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of temozolomide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the drug exposure.

Dermatologic: Toxic epidermal necrolysis and Stevens-Johnson syndrome

Immune System: Hypersensitivity reactions, including anaphylaxis. Erythema multiforme, which resolved after discontinuation of temozolomide and, in some cases, recurred upon rechallenge.

Hematopoietic: Prolonged pancytopenia, which may result in aplastic anemia and fatal outcomes.

Hepatobiliary: Fatal and severe hepatotoxicity, elevation of liver enzymes, hyperbilirubinemia, cholestasis, and hepatitis.

Infections: Serious opportunistic infections, including some cases with fatal outcomes, with bacterial, viral (primary and reactivated), fungal, and protozoan organisms.

Pulmonary: Interstitial pneumonitis, pneumonitis, alveolitis, and pulmonary fibrosis.

Endocrine: Diabetes insipidus

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]* and findings from animal studies, temozolomide can cause fetal harm when administered to a pregnant woman. Available postmarketing reports describe cases of spontaneous abortions and congenital malformations, including polymalformations with central nervous system, facial, cardiac, skeletal, and genitourinary system anomalies with exposure to temozolomide during pregnancy. These cases report similar adverse developmental outcomes to those observed in animal studies. Administration of temozolomide capsules to rats and rabbits during the period of organogenesis caused numerous external, internal, and skeletal malformations at doses less than the maximum human dose based on body surface area *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Five consecutive days of oral administration of temozolomide at doses of 75 and 150 mg/m^2 (0.38 and 0.75 times the human dose of 200 mg/m^2) in rats and rabbits, respectively, during the period of organogenesis (Gestation Days 8-12) caused numerous malformations of the external and internal organs and skeleton in both species. In rabbits, temozolomide at the 150 mg/m^2 dose (0.75 times the human dose of 200 mg/m^2) caused embryolethality as indicated by increased resorptions.

8.2 Lactation

There are no data on the presence of temozolomide or its metabolites in human milk, the effects on a breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions, including myelosuppression from temozolomide in the breastfed children, advise women not to breastfeed during treatment with temozolomide and for at least 1 week after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating temozolomide capsules *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Temozolomide capsules can cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with temozolomide capsules and for at least 6 months after the last dose.

Males

Because of the potential for embryofetal toxicity and genotoxic effects on sperm cells, advise male patients with pregnant partners or female partners of reproductive potential to use condoms during treatment with temozolomide capsules and for at least 3 months after the final dose *[see Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)]*.

Advise male patients not to donate semen during treatment with temozolomide capsules and for at least 3 months after the final dose.

Infertility

Temozolomide capsules may impair male fertility *[see Nonclinical Toxicology (13.1)]*. Limited data from male patients show changes in sperm parameters during treatment with temozolomide capsules; however, no information is available on the duration or reversibility of these changes.

8.4 Pediatric Use

Safety and effectiveness of temozolomide capsules have not been established in pediatric patients. Safety and effectiveness of temozolomide capsules were assessed, but not established, in 2 open-label studies in pediatric patients aged 3 to 18 years. In one study, 29 patients with recurrent brain stem glioma and 34 patients with recurrent high-grade astrocytoma were enrolled. In a second study conducted by the Children's Oncology Group (COG), 122 patients were enrolled, including patients with medulloblastoma/PNET (29), high grade astrocytoma (23), low grade astrocytoma (22), brain stem glioma (16), ependymoma (14), other CNS tumors (9), and non-CNS tumors (9). The adverse reaction profile in pediatric patients was similar to adults.

8.5 Geriatric Use

In the Newly Diagnosed Glioblastoma trial, Study MK-7365-051, 15% of patients were 65 years and older. This study did not include sufficient numbers of patients aged 65 years and older to determine differences in effectiveness from younger patients. No overall differences in safety were observed between patients ≥65 years and younger patients.

In the Refractory Anaplastic Astrocytoma trial, Study MK-7365-0006, 4% of patients were 70 years and older. This study did not include sufficient numbers of patients aged 70 years and older to determine differences in effectiveness from younger patients. Patients 70 years and older had a higher incidence of Grade 4 neutropenia (25%) and Grade 4 thrombocytopenia (20%) in the first cycle of therapy than patients less than 70 years of age *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

8.6 Renal Impairment

No dosage adjustment is recommended for patients with creatinine clearance (CLcr) of 36 to 130 mL/min/m^2 *[see Clinical Pharmacology (12.3)]*. The recommended dose of temozolomide has not been established for patients with severe renal impairment (CLcr < 36 mL/min/m^2) or for patients with end-stage renal disease on dialysis.

8.7 Hepatic Impairment

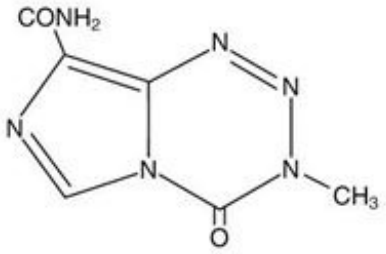
No dosage adjustment is recommended for patients with mild to moderate hepatic impairment (Child Pugh class A and B) *[see Clinical Pharmacology (12.3)]*. The recommended dose of temozolomide has not been established for patients with severe hepatic impairment (Child-Pugh class C).

10 OVERDOSAGE

Dose-limiting toxicity was myelosuppression and was reported with any dose but is expected to be more severe at higher doses. An overdose of 2000 mg per day for 5 days was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia, multi-organ failure, and death. There are reports of patients who have taken more than 5 days of treatment (up to 64 days), with adverse reactions reported including myelosuppression, which in some cases was severe and prolonged, and infections and resulted in death. In the event of an overdose, monitor complete blood count and provide supportive measures as necessary.

11 DESCRIPTION

Temozolomide is an alkylating drug. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-*as*-tetrazine-8-carboxamide. The structural formula of temozolomide is:



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5) and labile at pH >7; hence temozolomide can be administered orally and intravenously. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

Temozolomide Capsules, for oral use, contain either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of temozolomide.

The inactive ingredients are as follows: lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid.

The body of the capsules is made of gelatin and titanium dioxide, and are opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, and black iron oxide.

- *Temozolomide Capsules 5 mg:* The green cap contains gelatin, titanium dioxide, iron oxide yellow, and FD&C Blue #1.
- *Temozolomide Capsules 20 mg:* The gold cap contains gelatin and iron oxide yellow.
- *Temozolomide Capsules 100 mg:* The pink cap contains gelatin, titanium dioxide, FD&C Blue #1, D&C Red # 40 and FD&C Yellow #6
- *Temozolomide Capsules 140 mg:* The blue cap contains gelatin, FD&C Blue #1. D&C Red # 28 and FD&C Red #40.
- *Temozolomide Capsules 180 mg:* The dark orange cap contains gelatin, titanium dioxide, FD&C Blue #1, FD&C Red #40 and FD&C Yellow #6.
- *Temozolomide Capsules 250 mg:* The white opaque cap contains gelatin and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine.

12.3 Pharmacokinetics

Following a single oral dose of 150 mg/m^2, the mean C_{max} value for temozolomide was 7.5 mcg/mL and for MTIC was 282 ng/mL. The mean AUC value for temozolomide was 23.4 mcg·hr/mL and for MTIC was 864 ng·hr/mL.

Temozolomide exhibits linear kinetics over the therapeutic dosing range of 75 mg/m^2/day to 250 mg/m^2/day.

Absorption

The median T_{max} is 1 hour.

Effect of Food

The mean C_{max} and AUC decreased by 32% and 9%, respectively, and median T_{max} increased by 2-fold (from 1-2.25 hours) when temozolomide capsules were administered after a modified high-fat breakfast (587 calories comprised of 1 fried egg, 2 strips of bacon, 2 slices of toast, 2 pats of butter, and 8 oz whole milk).

Distribution

Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). The mean percent bound of drug-related total radioactivity is 15%.

Elimination

Clearance of temozolomide is about 5.5 L/hr/m^2 and the mean elimination half-life is 1.8 hours.

Metabolism

Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, MTIC and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively.

Excretion

About 38% of the administered temozolomide total radioactive dose is recovered over 7 days: 38% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is unchanged temozolomide (6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%).

Specific Populations

No clinically meaningful differences in the pharmacokinetics of temozolomide were observed based on age (range: 19-78 years), gender, smoking status (smoker vs. non-smoker), creatinine clearance (CLcr) of 36 to 130 mL/min/m^2, or mild to moderate hepatic impairment (Child Pugh class A and B). The pharmacokinetics of temozolomide has not been studied in patients with CLcr < 36 mL/min/m^2, end-stage renal disease on dialysis, or severe hepatic impairment (Child-Pugh class C).

Drug Interaction Studies

Effect of Other Drugs on Temozolomide Pharmacokinetics

In a multiple-dose study, administration of temozolomide capsules with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC.

A population analysis indicated that administration of valproic acid decreases the clearance of temozolomide by about 5%.

A population analysis did not demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, histamine-2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Temozolomide is carcinogenic in rats at doses less than the maximum recommended human dose. Temozolomide induced mammary carcinomas in both males and females at doses 0.13 to 0.63 times the maximum human dose (25-125 mg/m^2) when administered orally on 5 consecutive days every 28 days for 6 cycles. Temozolomide also induced fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate, carcinomas of the seminal vesicles, schwannomas of the heart, optic nerve, and harderian gland, and adenomas of the skin, lung, pituitary, and thyroid at doses 0.5 times the maximum daily dose. Mammary tumors were also induced following 3 cycles of temozolomide at the maximum recommended daily dose.

Temozolomide is a mutagen and a clastogen. In a reverse bacterial mutagenesis assay (Ames assay), temozolomide increased revertant frequency in the absence and presence of metabolic activation. Temozolomide was clastogenic in human lymphocytes in the presence and absence of metabolic activation.

Temozolomide impairs male fertility. Temozolomide caused syncytial cells/immature sperm formation at doses of 50 and 125 mg/m^2 (0.25 and 0.63 times the human dose of 200 mg/m^2) in rats and dogs, respectively, and testicular atrophy in dogs at 125 mg/m^2.

13.2 Animal Toxicology and/or Pharmacology

Toxicology studies in rats and dogs identified a low incidence of hemorrhage, degeneration, and necrosis of the retina at temozolomide doses equal to or greater than 125 mg/m^2 (0.63 times the human dose of 200 mg/m^2). These changes were most commonly seen at doses where mortality was observed.

14 CLINICAL STUDIES

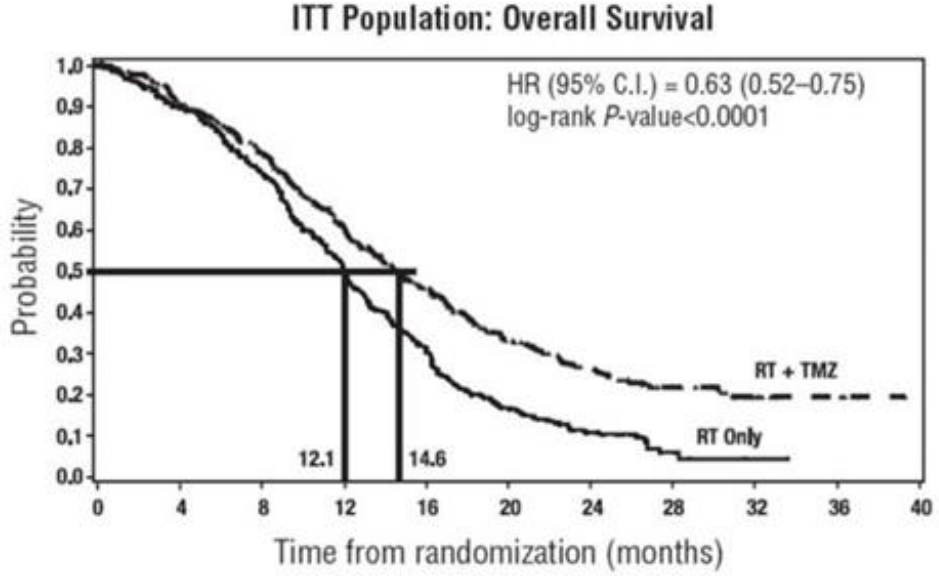
14.1 Newly Diagnosed Glioblastoma

The efficacy of temozolomide was evaluated in Study MK-7365-051, a randomized (1:1), multicenter, open-label trial. Eligible patients were required to have newly diagnosed glioblastoma. Patients were randomized to receive either radiation therapy alone or concomitant temozolomide 75 mg/m^2 once daily starting the first day of radiation therapy and continuing until the last day of radiation therapy for 42 days (with a maximum of 49 days), followed by temozolomide 150 mg/m^2 or 200 mg/m^2 once daily on Days 1 to 5 of each 28-day cycle, starting 4 weeks after the end of radiation therapy and continuing for 6 cycles. In both arms, focal radiation therapy was delivered as 60 Gy/30 fractions and included radiation to the tumor bed or resection site with a 2- to 3-cm margin. PCP prophylaxis was required during the concomitant phase, regardless of lymphocyte count and continued until recovery of lymphocyte count to grade 1 or less. The major efficacy outcome measure was overall survival.

A total of 573 patients were randomized, 287 to temozolomide and radiation therapy and 286 to radiation therapy alone. At the time of disease progression, temozolomide was administered as salvage therapy in 161 patients of the 282 (57%) in the radiation therapy alone arm and 62 patients of the 277 (22%) in the temozolomide and radiation therapy arm.

The addition of concomitant and maintenance temozolomide to radiation therapy for the treatment of patients with newly diagnosed glioblastoma showed a statistically significant improvement in overall survival compared to radiotherapy alone (**Figure 1**). The hazard ratio (HR) for overall survival was 0.63 (95% CI: 0.52, 0.75) with a log-rank *P*<0.0001 in favor of the temozolomide arm. The median survival was increased by 2.5 months in the temozolomide arm.

FIGURE 1: Kaplan-Meier Curves for Overall Survival (ITT Population) in Newly Diagnosed Glioblastoma Trial



14.2 Refractory Anaplastic Astrocytoma

The efficacy of temozolomide was evaluated in Study MK-7365-006, a single-arm, multicenter trial. Eligible patients had anaplastic astrocytoma at first relapse and a baseline Karnofsky performance status (KPS) of 70 or greater. Patients had previously received radiation therapy and may also have previously received a nitrosourea with or without other chemotherapy. Fifty-four patients had disease progression on prior therapy with both a nitrosourea and procarbazine and their malignancy was considered refractory to chemotherapy (refractory anaplastic astrocytoma population). Temozolomide capsules were given on Days 1 to 5 of each 28-day cycle at a starting dose of 150 mg/m^2/day. If ANC was ≥1.5 x 10^9/L and platelet count was ≥100 x 10^9/L at the nadir and on Day 1 of the next cycle, the temozolomide dose was increased to 200 mg/m^2/day. The major efficacy outcome measure was progression-free survival at 6 months and the additional efficacy outcome measures were overall survival and overall response rate.

In the refractory anaplastic astrocytoma population (n=54), the median age was 42 years (range: 19 to

76); 65% were male; and 72% had a KPS of >80. Sixty-three percent of patients had surgery other than a biopsy at the time of initial diagnosis. Of those patients undergoing resection, 73% underwent a subtotal resection and 27% underwent a gross total resection. Eighteen percent of patients had surgery at the time of first relapse. The median time from initial diagnosis to first relapse was 13.8 months (range: 4.2 months to 6.3 years).

In the refractory anaplastic astrocytoma population, the overall response rate (CR+PR) was 22% (12 of 54 patients) and the complete response rate was 9% (5 of 54 patients). The median duration of all responses was 50 weeks (range: 16 to 114 weeks) and the median duration of complete responses was 64 weeks (range: 52 to 114 weeks). In this population, progression-free survival at 6 months was 45% (95% CI: 31%, 58%) and progression-free survival at 12 months was 29% (95% CI: 16%, 42%). Median progression-free survival was 4.4 months. Overall survival at 6 months was 74% (95% CI: 62%, 86%) and 12-month overall survival was 65% (95% CI: 52%, 78%). Median overall survival was 15.9 months.

15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. http:www.osha.gov/SLTC/hazardousdrugs/index.

16 HOW SUPPLIED/STORAGE AND HANDLING

Temozolomide is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

Temozolomide Capsules are supplied in amber glass bottles with child-resistant polypropylene caps containing the following capsule strengths:

Temozolomide Capsules, 5 mg, have a green opaque cap and white opaque body. The capsule is imprinted with "AMG" on the cap and "252" on the body in black ink. They are supplied as follows:
5-count – NDC 43975-252-05
14-count – NDC 43975-252-14

Temozolomide Capsules, 20 mg, have a gold cap and white opaque body. The capsule is imprinted with "AMG" on the cap and "253" on the body in black ink. They are supplied as follows:
5-count – NDC 43975-253-05
14-count – NDC 43975-253-14

Temozolomide Capsules, 100 mg, have a pink opaque cap and white opaque body. The capsule is imprinted with "AMG" on the cap and "254" on the body in black ink. They are supplied as follows:
5-count – NDC 43975-254-05
14-count – NDC 43975-254-14

Temozolomide Capsules, 140 mg, have a blue cap and white opaque body. The capsule is imprinted with "AMG" on the cap and "255" on the body in black ink. They are supplied as follows:
5-count – NDC 43975-255-05
14-count – NDC 43975-255-14

Temozolomide Capsules, 180 mg, have a dark orange opaque cap and white opaque body. The capsule is imprinted with "AMG" on the cap and "256" on the body in black ink. They are supplied as follows:
5-count – NDC 43975-256-05
14-count – NDC 43975-256-14

Temozolomide Capsules, 250 mg, have a white opaque cap and body. The capsule is imprinted with "AMG" on the cap and "257" on the body in black ink. They are supplied as follows:
5-count – NDC 43975-257-05

Store temozolomide capsules at 20° to 25°C (68°F to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression

Inform patients that temozolomide capsules can cause low blood cell counts and the need for frequent monitoring of blood cell counts. Advise patients to contact their healthcare provider immediately for bleeding, fever, or other signs of infection *[see Warnings and Precautions (5.1)]*.

Myelodysplastic Syndrome and Secondary Malignancies

Advise patients of the increased risk of myelodysplastic syndrome and secondary malignancies *[see Warnings and Precautions (5.2)]*.

Pneumocystis Pneumonia

Advise patients of the increased risk of Pneumocystis pneumonia and to contact their healthcare provided immediately for new or worsening pulmonary symptoms. Inform patients that prophylaxis for Pneumocystis pneumonia may be needed *[see Dosage and Administration (2.1), Warnings and Precautions (5.3)]*.

Hepatotoxicity

Advise patients of the increased risk of hepatotoxicity and to contact their healthcare provider immediately for signs or symptoms of hepatoxicity *[see Warnings and Precautions (5.4)]*.

Administration Instructions

Advise patient to not open capsules. If capsules are accidentally opened or damaged, advise patients to take rigorous precautions with capsule contents to avoid inhalation or contact with the skin or mucous membranes. In case of powder contact, the hands should be washed *[see Dosage and Administration (2.3)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with temozolomide capsules and for at least 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Advise male patients with pregnant partners or female partners of reproductive potential to use condoms during treatment with temozolomide capsules and for at least 3 months after the final dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Advise male patients not to donate semen during treatment with temozolomide capsules and for at least 3 months after the final dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with temozolomide capsules and for at least 1 week after the final dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that temozolomide capsules may impair fertility *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Distributed by:
Amerigen Pharmaceuticals, Inc.
Lyndhurst, NJ 07071 USA

1-877-220-3784

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Patient Information
Temozolomide (te moe zoe' loe mide) Capsules

What is the most important information I should know about Temozolomide Capsules?
Temozolomide Capsules may cause birth defects.
Females and female partners of male patients who take temozolomide capsules:

- Avoid becoming pregnant while taking temozolomide capsules.
- Females who can become pregnant should use an effective form of birth control (contraception) during treatment and for at least 6 months after your last dose of temozolomide capsules. Your doctor should to do a pregnancy test to make sure that you are not pregnant before you start taking temozolomide capsules.
- Tell your doctor right away if you become pregnant or think you are pregnant during treatment with temozolomide capsules.

Males taking temozolomide capsules and have a female partner who is pregnant or who can become pregnant:

- Use a condom for birth control (contraception) during treatment and for at least 3 months after taking your final dose of temozolomide capsules.
- Do not donate semen during treatment and for at least 3 months after your final dose of temozolomide capsules.

See the section "What are the possible side effects of Temozolomide Capsules?" for more information about side effects.

What are Temozolomide Capsules?
Temozolomide capsules are a prescription medicine used to treat adults with certain brain cancer tumors.
It is not known if temozolomide capsules are safe and effective in children.

Who should not take Temozolomide Capsules?
Do not take temozolomide capsules if you:

- have had an allergic reaction to temozolomide or any of the other ingredients in temozolomide capsules. See the end of this leaflet for a list of ingredients in temozolomide capsules. Symptoms of an allergic reaction with temozolomide capsules may include: a red itchy rash, or a severe allergic reaction, such as trouble breathing, swelling of the face, throat, or tongue, or severe skin reaction. If you are not sure, ask your doctor.
- have had an allergic reaction to dacarbazine (DTIC), another cancer medicine.

What should I tell my doctor before taking Temozolomide Capsules?
Tell your doctor about all your medical conditions, including if you:

- have kidney problems
- have liver problems
- are pregnant or plan to become pregnant. **See "What is the most important information I should know about Temozolomide Capsules?"**
- are breast-feeding or plan to breastfeed. It is not known if temozolomide passes into breast milk. **Do not** breastfeed during treatment and for at least 1 week after your last dose of temozolomide capsules.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take a medicine that contains valproic acid.
Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take Temozolomide?
Temozolomide may be taken two different ways:

- you may take temozolomide by mouth as a capsule, **or**
- you may receive temozolomide as an intravenous (IV) injection into a vein.

Your doctor will decide the best way for you to take temozolomide. Take temozolomide exactly as prescribed by your doctor.
There are two common dosing schedules for taking temozolomide depending on the type of brain cancer tumor that you have.

- People with certain brain cancer tumors take or receive temozolomide:
    - One time each day for 42 days in a row (possibly 49 days depending on side effects) along with receiving radiation treatment. **This is one cycle of treatment.**
    - After this, your doctor may prescribe 6 more cycles of temozolomide as "maintenance" treatment. For each of these cycles, you take or receive temozolomide one time each day for 5 days in a row and then you stop taking it for the next 23 days. **This is a 28-day maintenance treatment cycle.**
- People with certain other brain cancer tumors take or receive temozolomide:
    - One time each day for 5 days in a row only, and then stop taking it for the next 23 days. **This is one cycle of treatment (28 days).**
    - Your doctor will watch your progress on temozolomide and decide how long you should take it. You might take temozolomide until your tumor gets worse or for possibly up to 2 years.
- If your doctor prescribes a treatment regimen that is different from the information in this leaflet, make sure you follow the instructions given to you by your doctor.
- Your doctor may change your dose of temozolomide, or tell you to stop temozolomide for a short period of time or permanently if you have certain side effects.
- Your doctor will decide how many treatment cycles of temozolomide that you will receive, depending on how you respond to and tolerate treatment.

Temozolomide Capsules:

- Take temozolomide capsules exactly as your doctor tells you to.
- Temozolomide capsules contain a white capsule body with a color cap and the colors vary based on the dosage strength. Your doctor may prescribe more than one strength of temozolomide capsules for you, so it is important that you understand how to take your medicine the right way. Be sure that you understand exactly how many capsules you need to take on each day of your treatment, and what strengths to take. **This may be different whenever you start a new cycle.**
- **Do not** take more temozolomide capsules than prescribed.
- Talk to your doctor or pharmacist before taking your dose if you are not sure how much

temozolomide to take. This will help to prevent taking too much temozolomide and decrease your chances of getting serious side effects.

- Take each day's dose of temozolomide capsules at one time, with a full glass of water.
- **Swallow temozolomide capsules whole.** Do not chew, open, or split the capsules.
- Take temozolomide capsules at the same time each day.
- Take temozolomide capsules the same way each time, either with food or without food.
- If temozolomide capsules are accidentally opened or damaged, be careful not to breathe in (inhale) the powder from the capsules or get the powder on your skin or mucous membranes (for example, in your nose or mouth). If contact with any of these areas happens, flush the area with water.
- To help reduce nausea and vomiting, try to take temozolomide capsules on an empty stomach or at bedtime. Your doctor may prescribe medicine to help prevent or treat nausea, or other medicines to reduce side effects with temozolomide capsules.
- See your doctor regularly to check your progress. Your doctor will check you for side effects.
- If you take more temozolomide capsules than prescribed, call your doctor or get emergency medical help right away.

What are the possible side effects of Temozolomide Capsules?
Temozolomide capsules can cause serious side effects, including:

- **See "What is the most important information I should know about Temozolomide Capsules?"**
- **Decreased blood cell counts.** Temozolomide capsules can affect your bone marrow and cause you to have decreased blood cell counts. Decreased white blood cell count, red blood cell count and platelet count are common with temozolomide capsules but it can also be severe and lead to death.
    - Your doctor will do blood tests regularly to check your blood cell counts before you start and during treatment with temozolomide capsules.
    - Your doctor may need to change the dose of temozolomide capsules, or when you get it depending on your blood cell counts.
    - **People who are age 70 or older and women have a higher risk for developing decreased blood cell counts during treatment with temozolomide capsules.**
- **Secondary cancers.** Blood problems such as myelodysplastic syndrome (MDS) and new cancers (secondary cancers), including a certain kind of leukemia, can happen in people who take temozolomide capsules. Your doctor will monitor you for this.
- **Pneumocystis pneumonia (PCP).** PCP is an infection that people can get when their immune system is weak. Temozolomide capsules decrease white blood cells, which makes your immune system weaker and can increase your risk of getting PCP.
    - People who are taking steroid medicines or who stay on temozolomide capsules for a longer period of time may have an increased risk of getting PCP infection.
    - Anyone who takes temozolomide capsules will be watched carefully by their doctor for low blood cell counts and this infection.
    - Tell your doctor if you have any of the following signs and symptoms of PCP infection: shortness of breath, or fever, chills, dry cough.
- **Liver problems. Liver problems can happen with temozolomide capsules and can sometimes be severe and lead to death.** Your doctor will do blood tests to check your liver

function before you start taking temozolomide capsules, during treatment, and about 2 to 4 weeks after your last dose of temozolomide capsules.

Common side effects of temozolomide capsules include:

- hair loss
- feeling tired
- nausea and vomiting
- headache
- constipation
- loss of appetite
- convulsions
- rash
- diarrhea
- unable to move (paralysis) on one side of the body
- weakness
- fever
- dizziness
- coordination problems
- viral infection
- memory loss
- sleep problems

Temozolomide Capsules can affect fertility in males and may affect your ability to father a child. Talk with your doctor if fertility is a concern for you.

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the possible side effects with temozolomide capsules. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Temozolomide Capsules?

- Store temozolomide capsules at room temperature between 68°F to 77°F (20° to 25°C).
- **Keep temozolomide capsules and all medicines out of the reach of children.**

General information about the safe and effective use of temozolomide capsules.
Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use temozolomide capsules for a condition for which it was not prescribed. Do not give temozolomide capsules to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about temozolomide capsules. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about temozolomide capsules that is written for health professionals.

What are the ingredients in Temozolomide Capsules?

Active ingredient: temozolomide

Inactive ingredients: lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid and stearic acid.

The body of the capsules is made of gelatin and titanium dioxide, and is opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia, potassium hydroxide, and black iron oxide.

Temozolomide Capsules 5 mg: The green cap contains gelatin, titanium dioxide, iron oxide yellow, and FD&C Blue #1.
Temozolomide Capsules 20 mg: The gold cap contains gelatin and iron oxide yellow.
Temozolomide Capsules 100 mg: The pink cap contains gelatin, titanium dioxide, FD&C Blue #1, FD&C Red # 40 and FD&C Yellow #6
Temozolomide Capsules 140 mg: The blue cap contains gelatin, FD&C Blue #1, D&C Red # 28 and FD&C Red #40.
Temozolomide Capsules 180 mg: The dark orange cap contains gelatin, titanium dioxide, FD&C Blue #1, FD&C Red #40 and FD&C Yellow #6.
Temozolomide Capsules 250 mg: The white opaque cap contains gelatin and titanium dioxide.

Distributed by:
Amerigen Pharmaceuticals, Inc.
Lyndhurst, NJ 07071 USA
1-877-220-3784

MG1026/03 Revised 02/2020

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: February 2020

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

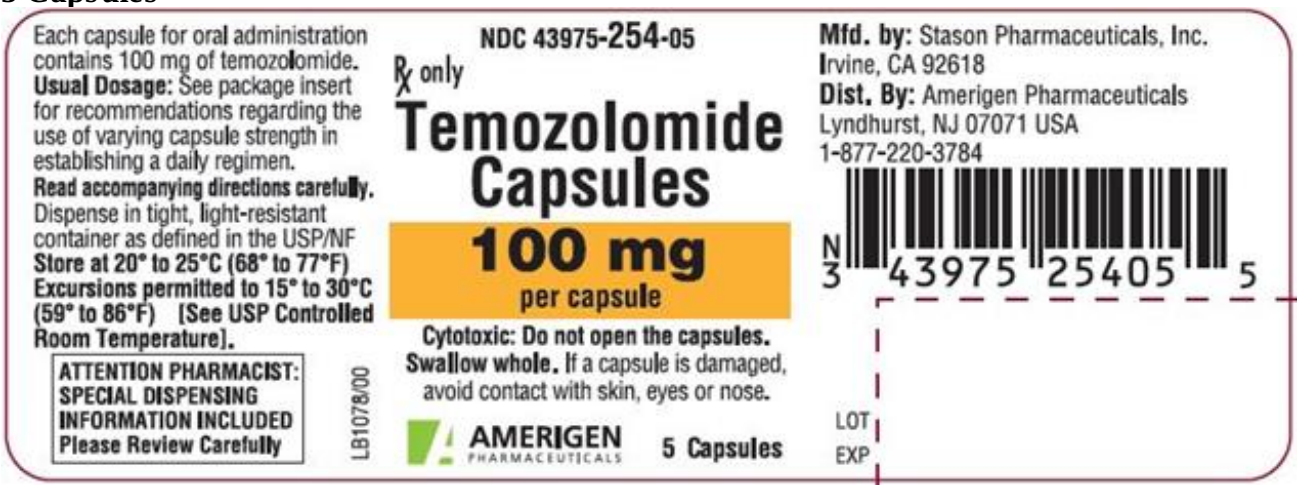
Temozolomide Capsules, 5 mg per capsule
NDC 43975-252-05
Rx only
Cytotoxic: Do not open the capsules.
Swallow whole. If a capsule is damaged, avoid contact with skin, eyes or nose.
5 Capsules

Package/Label Display Panel

Temozolomide Capsules, 20 mg per capsule
NDC 43975-253-05
Rx only
Cytotoxic: Do not open the capsules.
Swallow whole. If a capsule is damaged, avoid contact with skin, eyes or nose.
5 Capsules

Package/Label Display Panel

Temozolomide Capsules, 100 mg per capsule
NDC 43975-254-05
Rx only
Cytotoxic: Do not open the capsules.
Swallow whole. If a capsule is damaged, avoid contact with skin, eyes or nose.
5 Capsules



Package/Label Display Panel

Temozolomide Capsules, 140 mg per capsule
NDC 43975-255-05
Rx only
Cytotoxic: Do not open the capsules.
Swallow whole. If a capsule is damaged, avoid contact with skin, eyes or nose.
5 Capsules

Package/Label Display Panel

Temozolomide Capsules, 180 mg per capsule
NDC 43975-256-05
Rx only
Cytotoxic: Do not open the capsules.
Swallow whole. If a capsule is damaged, avoid contact with skin, eyes or nose.
5 Capsules

Package/Label Display Panel

Temozolomide Capsules, 250 mg per capsule
NDC 43975-257-05
Rx only
Cytotoxic: Do not open the capsules.
Swallow whole. If a capsule is damaged, avoid contact with skin, eyes or nose.
5 Capsules

TEMOZOLOMIDE

temozolomide capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43975-252
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TARTARIC ACID (UNII: W4888I119H)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	

Product Characteristics			
Color	WHITE (opaque body) , GREEN (opaque cap)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	AMG252
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:43975-252-05	5 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	07/13/2016	
2	NDC:43975-252-14	14 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	07/13/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203490	07/13/2016	

TEMOZOLOMIDE

temozolomide capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43975-253
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	20 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TARTARIC ACID (UNII: W4888I119H)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	

AMMONIA (UNII: 5138Q19F1X)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FERRIC OXIDE YELLOW (UNII: EX43802MRT)	

Product Characteristics			
Color	YELLOW (gold clear cap) , WHITE (opaque body)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	AMG253
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43975-253-05	5 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	07/13/2016	
2	NDC:43975-253-14	14 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	07/13/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203490	07/13/2016	

TEMOZOLOMIDE

temozolomide capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43975-254
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	100 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TARTARIC ACID (UNII: W4888I119H)	
STEARIC ACID (UNII: 4ELV7Z65AP)	

GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics

Color	WHITE (opaque body) , PINK (opaque cap)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	AMG254
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43975-254-05	5 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	07/13/2016	
2	NDC:43975-254-14	14 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	07/13/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203490	07/13/2016	

TEMOZOLOMIDE

temozolomide capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43975-255
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	140 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TARTARIC ACID (UNII: W4888I119H)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
D&C RED NO. 28 (UNII: 767IP0Y5NH)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	

Product Characteristics			
Color	WHITE (opaque body) , BLUE (clear cap)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	AMG255
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:43975-255-05	5 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	07/13/2016	
2	NDC:43975-255-14	14 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	07/13/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203490	07/13/2016	

TEMOZOLOMIDE

temozolomide capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43975-256
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	180 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TARTARIC ACID (UNII: W4888I119H)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	

Product Characteristics

Color	WHITE (opaque body) , ORANGE (dark opaque cap)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	AMG256
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43975-256-05	5 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	07/13/2016	
2	NDC:43975-256-14	14 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	07/13/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

ANDA	ANDA203490	07/13/2016	

TEMOZOLOMIDE

temozolomide capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43975-257
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	250 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TARTARIC ACID (UNII: W4888I119H)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
ALCOHOL (UNII: 3K9958V90M)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics			
Color	WHITE (opaque cap) , WHITE (opaque body)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	AMG257
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:43975-257-05	5 in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	07/13/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203490	07/13/2016	

Labeler - ANI Pharmaceuticals, Inc. (145588013)

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